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Early Management of Severe Acute Pancreatitis

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Abstract Significant literature on the management of acute severe acute pancreatitis has emerged in recent years. The new information ranges from data on newer single or multiparameter severity assessment tools and classification systems to therapeutic modalities. However, a few basic issues—the ideal severity assessment modality, volume of intravenous fluids required in the first 48 to 72 h, and the role of prophylactic antibiotics—are still not clear and are subject to controversy. The International Working Group has devised the Revised Atlanta Classification, which will be published soon. This new classification is eagerly awaited worldwide, and hopefully clarifies many of the problems of the original Atlanta Classification. In this article, we discuss the developments that have arisen in the past 2 to 3 years concerning the classification, prognostication, and early management of severe acute pancreatitis.

Keywords Severe acute pancreatitis · Early management · Severity assessment · Bedside assessment for severity in acute pancreatitis · Systemic inflammatory response syndrome · Infected pancreatic necrosis · Persistent organ failure · Moderately severe acute pancreatitis · Early severe acute pancreatitis · Critical pancreatitis · Fluid management · Prophylactic antibiotics

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Introduction

Acute pancreatitis (AP) is a clinical enigma. Despite rapid progress in the understanding of the disease, both at the experimental and the clinical level, specific treatment still eludes the medical literature. Even though the overall mortality rate among patients of AP per 1,00,000 persons remains the same, the global incidence of AP has been steadily increasing [1]. AP begins as a localized pancreatic and peripancreatic inflammation, and is usually accompanied by a compensatory anti-inflammatory response syndrome (CARS). Failure of the local protective responses leads to amplification and extension of the local inflammatory mediators into the systemic circulation, thereby leading to a systemic inflammatory response syndrome (SIRS) [2]. SIRS, along with increased tissue fluid and impairment of the microcirculation, leads to multiple organ dysfunction and eventually multi-organ failure, which is associated with very high mortality (~ 47%) [3]. On the other hand, excessive CARS will render the immune functions inefficient, leading to increased susceptibility to infections. Moreover, a state of immunoparalysis can exist in AP, as manifested by a reduction in HLA-DR expression [4].

In this review, we discuss the major developments in the classification, prognostication, and early management of severe acute pancreatitis (SAP), primarily from the past 2 to 3 years, that appeared in peer-reviewed English literature (Pubmed, Medline, Cochrane database), mostly in the form of meta-analysis, randomized controlled trials (RCTs), consensus guidelines, scholarly reviews, and expert opinions.

Severity Definitions

For almost the past two decades, AP severity was described on the basis of the Atlanta Classification of 1992 [5].

However, many aspects of the criteria lacked clarity, especially in definitions of organ failure (OF), lack of differentiation between transient and persistent OF, and definitions of local complications (eg, fluid collections, necrosis, pseudocysts) [3]. These flaws led to infrequent use of the original Atlanta Classification in the research and clinical settings. In fact, a recent review of 447 articles showed wide variations in the interpretations of the Atlanta definitions [6•]. To overcome these issues, the International Working Group recently developed a revised classification of AP, in which two discrete phases of AP were described. Moreover, more plausible definitions of local complications like acute post-necrotic collections, walled-off pancreatic necrosis, and acute peripancreatic fluid collections were proposed, and newer severity assessment tools (eg, the Marshall and sequential organ failure assessment [SOFA] scoring systems) were incorporated. The new criteria are going to be published soon.

Over the past few years, it was observed in individual studies that mortality in acute pancreatitis without OF is usually low. This finding means that death in patients with necrotizing pancreatitis is largely related to OF [3, 7]. Persistence of organ failure beyond 48 h is associated with a mortality of 34% to 55%, whereas resolution within 48 h is associated with a mortality of 0% to 3% [8, 9]. However, a recent meta-analysis of 14 studies (both prospective and retrospective) involving 1478 patients and spanning more than 10 years showed that mortality is similar in patients with only OF or infected pancreatic necrosis (IPN) (30% and 32%, respectively). When both OF and IPN are present, mortality increased to 43%. Even though the individual studies in this meta-analysis were mostly observational, lacked uniformity in defining OF, and did not address the duration of OF in a uniform manner, the analysis suggests that presence of either OF or IPN indicates severe disease; moreover, the presence of both OF and IPN (seen in 24% of patients) points toward a synergy leading to even more severe disease. The authors conclude that this synergy justifies the introduction of a new subcategory of SAP, called critical AP (CAP) [10•].

Although the Atlanta Classification recognized only two types of AP (mild and severe), it soon became clear that AP is a group of heterogeneous clinical types. Isenmann et al. [11] first introduced another subgroup, called early severe AP (ESAP), in which OF was present in the first 72 h of AP and was associated with higher morbidity and mortality. Subsequently, we observed that patients without persistent OF, but with local complications (pancreatic parenchymal necrosis, discrete fluid collections, and pseudocysts), behaved differently from patients with OF (SAP) and those with neither OF or local complications (mild AP). Based on this premise, we recently characterized and prospectively validated a new subgroup of AP, namely, moderately severe acute pancreatitis (MSAP) [12•, 13]. In this discrete group of AP, the patients' requirement of intensive care unit (ICU) treatment and mortality is significantly lower than those with persistent OF with or without local complications (ie, SAP). On the other hand, the total hospital stay and requirement of interventions for local complications in patients with MSAP are similar to those with SAP.

Meanwhile, the ESAP subgroup was further subcategorized into fulminant and subfulminant AP by Sharma et al. [14]. They extended the period up to 7 days, and classified those with OF within 72 h as fulminant and those with OF between days 4 and 7 as subfulminant. Mortality among those with fulminant AP was 90% and among those with subfulminant AP was 73%. Patients who develop persistent OF after 7 days of onset were defined as late severe acute pancreatitis. This subclassification appears logical because AP is a dynamic disease; although patients may present with OF or may develop OF during the first week of hospital stay, IPN is usually seen from the second week and may be a cause of late OF during hospitalization. The subgroup of patients with late severe acute pancreatitis who have both OF and IPN belongs to the group with critical AP, as proposed by Petrov and Windsor [15] in their four-tier classification.

Based on these different categories of severity, we propose a new classification scheme for AP (Table 1). Uniform and clinically relevant definitions, along with a disease dynamics–guided categorization of AP, are essential from the standpoint of clinical assessment, setting thresholds for specific interventions, communicating with patient and caregiver, and establishing homogeneity in clinical research.

Severity Assessment

AP is a dynamic process, and an early assessment of severity and prediction of development of severe disease is essential for initiating tailor-made treatment. The traditionally used severity assessment tools (eg, Ranson's criteria, the Acute Physiology and Chronic Health Evaluation [APACHE] II criteria) were not free from problems and none were ideal. This situation mandated the development of newer and more objective assessment tools that would predict or gauge the severity of AP accurately. An ideal severity assessment tool would be simple, reproducible, applicable at any level of patient care, with few parameters, and inexpensive.

Recently, a new tool called the Bedside Assessment for Severity in Acute Pancreatitis or BISAP (blood urea nitrogen [BUN] >25 mg/dL, impaired mental status [Glasgow coma scale score <15], SIRS score ≥2, age > 60 years, and pleural effusion) was introduced to assess and

Table 1 Proposed classification of acute pancreatitis

A. Mild acute pancreatitis
Acute pancreatitis without persistent organ failure and local complications
B. Moderately severe acute pancreatitis
Acute pancreatitis without persistent organ failure but with local complications (pancreatic necrosis and/or peripancreatic collections)
C. Severe acute pancreatitis
i. Early severe acute pancreatitis
a. Fulminant acute pancreatitis
Acute pancreatitis with development of persistent organ failure within 72 h of onset
b. Subfulminant acute pancreatitis
Acute pancreatitis with development of persistent organ failure between 4 and 7 days of onset
ii. Late severe acute pancreatitis
Acute pancreatitis with development of severe disease (persistent organ failure or infected pancreatic necrosis) after 7 days of onset
D. Critical acute pancreatitis—Acute pancreatitis with both persistent organ failure and infected pancreatic necrosis

predict various outcome parameters of AP [16]. This five-point scoring system was derived from a multicenter cohort of more than 18,000 patients, and was validated in a similar number. An increase in the BISAP score was shown to be associated with increased mortality, and the predictive accuracy of mortality was found to be similar to that of the APACHE II system (receiver operating characteristic area under curve of APACHE II scoring vs BISAP is 0.82; 95% CI, 0.80–0.85, and 0.83; 95% CI, 0.80–0.83, respectively). Subsequently, studies have also shown that BISAP can predict persistent OF and necrosis ($P<0.0001$ and 0.0004) [17]. A recent study that compared the prognostic accuracy of the BISAP system with other existing systems (eg, Ranson's criteria, APACHE II, and CT severity index [CTSI]) concluded that, when used to assess persistent organ dysfunction, pancreatic necrosis, and mortality, BISAP was similar to the others in terms of simplicity and accuracy [18]. Although the components of this system are clinically relevant, easy to obtain, and appear to be applicable in a community setting, the requirement to assess 10 components of the five variables may not be appealing.

The other recently described severity assessment tool is the Harmless Acute Pancreatitis Score (HAPS) [19], which consists of rebound tenderness and/or guarding, serum creatinine, and hematocrit. According to this system, absence of rebound tenderness and/or guarding along with a normal hematocrit and serum creatinine level can predict a mild course of AP with an accuracy of 98%. Because the components are very simple and do not require expertise for interpretation, HAPS can be used with confidence even by a nonspecialist at the community level. However, this study did not address the in-hospital course of these patients. Therefore, before extrapolating the results to all patients with absence of rebound tenderness and/or guarding, along with a normal hematocrit and serum creatinine level, further studies to evaluate the natural history of these patients need to be conducted.

The role of SIRS score as an early predictor of AP severity is being increasingly recognized. An earlier study showed that a SIRS score≥2 over 48 h predicts a mortality of 25% [20]. A recent prospective study of more than 250 patients showed that those with higher SIRS scores within 24 h of presentation had significantly higher rates for various outcomes (eg, persistent organ failure, pancreatic necrosis, need for ICU care, and mortality) [21]. Another recent study supported the role of early SIRS scores in predicting adverse outcomes in patients with AP [22]. We have shown in a prospective cohort of 274 patients that a SIRS score≥2 at the time of admission increases the risk of subsequent development of primary intra-abdominal infections in necrotic pancreatic and/or peripancreatic tissues by 3.37-fold (95% CI, 1.37–8.65) [23].

Other multiparameter severity assessment tools such as the Panc 3 score [24] and the new Japanese Severity Score [25] were also described recently. However, these systems are limited by the retrospective study design, small sample size, and/or inclusion of many variables.

Hemoconcentration during the early phase of AP appears to be instrumental in the development of adverse outcomes [26]. Hematocrit and BUN are simple and reproducible markers of hemoconcentration. A recent study showed that hematocrit of 44% or more and/or hemoglobin of 14.6 g/dL early in the course of AP was associated with a 7.4-fold increase (95% CI, 1.6–35.4) in the risk of death among transferred patients [27]. This signifies the importance of initiating aggressive fluid therapy as early as possible in the management of AP. A similar study showed that a low admission hematocrit (≤ 44.8%) was associated with a significantly lower incidence of necrosis [28]. This study also suggested an admission serum creatinine of≥1.8 mg/dL as a marker of necrosis.

The importance of BUN as a single valuable marker of mortality was shown in a recent, large (n=13,384), multicenter, hospital-based cohort [29]. In this study, among the variables tested, only admission BUN was found to be an independent predictor of mortality (adjusted OR 2.9; 95% CI, 1.8–4.8). Besides this, for every 5-mg/dL increase in BUN, a 2.2-fold (95% CI, 1.9–2.9) increase in the adjusted OR for mortality was observed. Similar findings were shown in another recent study in a German cohort of 118 patients, in which an elevated admission BUN (cutoff at 33 mg/dL) was associated with a prolonged ICU stay (positive predictive value [PPV] 89%; negative predictive value [NPV] 62%) and mortality (PPV 67%; NPV 82%) [30]. However, the problems with this study were its retrospective nature, and only 44 patients had severe acute necrotizing pancreatitis.

Diagnosis of Local Complications

Local complications of AP include pancreatic parenchymal and peripancreatic necrosis, peripancreatic collections, and pancreatic pseudocysts. Although contrast-enhanced computed tomography (CECT) reliably detects pancreatic parenchymal necrosis and differentiates walled-off pancreatic necrosis [31], MRI can better detect necrotic debris within peripancreatic collections [32]. However, because MRI is expensive and may not be possible with the acutely sick patient, CECT is the modality that is still relied upon to evaluate peripancreatic collections. In view of the poor interobserver variability in defining the terminology for peripancreatic collections described in the original Atlanta Classification [33], an international interobserver agreement study was conducted using a new set of terminology. This study showed good to excellent interobserver agreement in defining the new set of morphologic terms to describe peripancreatic collections [34]. However, using correlative analysis between CECT and intraoperative findings of peripancreatic collections, we found that CECT has a limited role in differentiating peripancreatic collections into those containing necrosis with pus, necrosis without pus, and fluid without necrosis. Moreover, no single CECT finding can suggest the presence of infection in a necrotic collection without pus [35].

The role of endoscopic ultrasound (EUS) during an episode of AP is limited and still evolving. EUS during an episode of AP can be of help in detecting common bile duct stones when transabdominal ultrasound and CT fail; thus, it can guide therapy. Preliminary data suggest that certain features of EUS might be able to predict the severity of AP and diagnose necrosis more accurately, but this needs further validation [36].

Treatment

Fluid Management

Probably the most important and potentially effective treatment in the early management of AP is adequate fluid therapy. An effective circulating volume and adequate perfusion pressure are necessary to maintain pancreatic microcirculation, which could help in retarding the progression of the disease and in preventing the development of local complications. Unfortunately, no well-designed studies that specifically discuss the type and volume of fluid, rate of infusion, and parameters to titrate the infused fluid volume are available in the literature. Most experts recommend a fluid volume of more than 250 to 300 mL/h, at least for the first 48 h, or a volume adequate to maintain a urine output≥0.5 mL/kg body weight per hour. Our group retrospectively showed that a significant reduction of in-hospital mortality (0% vs 18%; P<0.04) resulted after infusing 33% of the first 72 h of fluid volume required within 24 h of presentation [37]. However, this study does not suggest or specify a definite fluid volume that needs to be transfused during the first 72 h. Further RCTs using different fluid volumes and infusion rates early in the disease course need to be considered. A recent study showed that very rapid hemodilution (hematocrit maintained at <35%) was associated with an increase in the rate of sepsis and in-hospital mortality compared to those with slow hemodilution (hematocrit maintained at ≥35%) [38]. However, the results of this study should be interpreted with caution because all these patients were also treated with Chinese traditional and herbal medicines in addition to currently unconventional treatment modalities (eg, newer generation antibiotics and somatostatin).

Nutrition

Metabolically, AP is characterized by a hypercatabolic state akin to severe sepsis, in which exogenous glucose fails to inhibit gluconeogenesis and there is increased energy expenditure, insulin resistance, and increased dependence on fatty acid oxidation to provide energy substrates. It has been shown that the pancreas is in a state of unresponsiveness during an acute episode of AP, and the secretion of trypsin is reduced. This finding negates the previously held concept of providing the pancreas rest by withholding enteral nutrition (EN) until the patient feels better. Even though there are no adequately powered trials to suggest specific times to start EN, it should be started as early as possible during the course of SAP. This is particularly important because EN improves gut mucosal barrier function, thereby reducing bacterial translocation and development of local complications (eg, infection of

pancreatic or peripancreatic necrosis or collections). Recent meta-analyses that compared EN to parenteral nutrition (PN) showed that EN can significantly reduce infection-related mortality [1]. A recent meta-analysis of two RCTs studied the best route for EN and concluded that both nasogastric and nasojejunal routes are similar in safety and tolerability, thereby implying that the nasogastric route may be used safely [1]. However, in view of the inadequate power and other issues of methodology, more adequately powered RCTs need to be performed; one such study is now under way to settle the issue.

Data are still scant regarding the type of EN (elemental, semielemental, or polymeric) and incorporation of immunomodulatory diet, probiotics, and supplements (eg, glutamine). It is widely believed that the elemental or semielemental diet (amino acids, maltodextrin, and medium- and long-chain triglycerides) is better absorbed and tolerated compared to the polymeric diet (nonhydrolyzed proteins, maltodextrin, oligofructosaccharide, and long-chain triglycerides), which is much less expensive. However, a recent meta-analysis of 20 RCTs involving more than 1000 patients showed no differences in tolerance, infectious complications, and mortality between semielemental diet and polymeric diet. Moreover, the addition of immunoenhancing ingredients (eg, glutamine, arginine, and omega-3 fatty acids) was not found to confer any additional benefit in clinical outcomes [39].

Even though probiotics are often used in SAP, a randomized, double-blind, placebo-controlled trial (the Probiotics in Pancreatitis Trial [PROPATRIA]) found that in patients with predicted SAP, probiotics did not reduce infectious complications, and instead were associated with increased mortality [40]. It was not clear if this finding was associated with the particular strain of organism used, and the trial is currently subject to ethical concerns. In a substudy of PROPATRIA, it was shown that among the patients with SAP and OF, the probiotic preparation was associated with an increase in enterocyte damage and increased bacterial translocation [41].

Although EN is the currently recommended route of nutrition in SAP, the only indication for PN is the inability to tolerate the targeted nutritional requirement by EN under circumstances like gut failure, prolonged ileus, complex pancreatic fistulae, and abdominal compartment syndrome. PN should be started after adequate hydration and hemodynamic stabilization. Although there are no specific contraindications to the use of PN, lipid administration in PN should be avoided completely in hypertriglyceridemia-associated AP. Once the patient's tolerance to EN increases, PN should be tapered [42].

Management of Pancreatic Necrosis

Pancreatic necrosis can be seen in 10% to 15% of patients with AP, out of which 33% (16%–47%) may develop infected necrosis. Infection of necrotic pancreatic tissue usually develops after the second week. Clinical guidelines and expert opinions do not recommend use of prophylactic antibiotics in the early phase of SAP; however, this guideline is seldom followed in clinical practice. In the past 5 years, at least eight meta-analyses of RCTs were performed on the role of prophylactic antibiotics, which showed divergent results in reducing overall sepsis, mortality, and development of pancreatic and peripancreatic infections. The major problems of the individual studies were heterogeneity in study design in terms of quality, choice of antibiotics, selection criteria, and outcome measures [1]. The most recent systematic review analyzed seven RCTs, including two double-blind RCTs, involving a total of 404 patients. Overall, compared to controls, prophylactic antibiotics did not reduce mortality (14.4% vs 8.4%), development of infected pancreatic necrosis (24.4% vs 19.7%), and nonpancreatic infections (36% vs 32.7%). When β-lactams and quinolones plus imidazoles were independently analyzed, no significant reduction was seen in mortality and infected pancreatic necrosis. In patients receiving imipenem, even though there was no reduction in mortality, development of pancreatic infection was found to be significantly less (RR 0.34, 95% CI, 0.13–0.84; $P<0.02$) [43].However, imipenem was used in only three studies, and the sample sizes were small. Therefore, use of prophylactic antibiotics in SAP remains controversial, and we currently do not recommend routine use of antibiotic prophylaxis. Moreover, overuse of antibiotics has the potential to cause secondary fungal infections. Fungal infections have been found to significantly increase morbidity in the form of longer hospital stay (63 vs 37 days; $P< 0.01$), longer ICU stay (28 vs 9 days; $P<0.01$), and higher OF rate (73 vs 47%; $P<0.04$) when compared to bacterial infections [44]. One group of patients in whom we feel 7 to 10 days of carbapenem prophylaxis might be useful are those with pancreatic necrosis with OF. These patients are at a high risk of developing critical AP (OF with infected pancreatic necrosis), which is associated with a mortality of 43%. By treating these patients with prophylactic imipenem, which has a good penetration and efficacy factor in the human pancreas [45], one might prevent development of critical AP. However, this needs to be tested in a RCT. The second group of patients who might benefit from antibiotic prophylaxis are those who look septic and in whom a source of infection is being sought. In these patients, antibiotics should be discontinued if no source of infection is found.

A detailed discussion of treatment modalities after infection of necrotic tissue has set in (a late event) is beyond the scope of this review. However, it is worth mentioning that more focus is currently being directed toward a primary conservative approach [46]. Among the

nonconservative modalities, several effective minimally invasive techniques, including direct endoscopic necrosectomy, have been described [47, 48].

Early Endoscopic Retrograde Cholangiopancreatography in Acute Biliary Pancreatitis

Until recently, early endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy was recommended for most patients with acute biliary pancreatitis. However, the most recent meta-analysis showed no reduction in complications and mortality from biliary AP with early ERCP and endoscopic sphincterotomy (24–72 h) in the absence of cholangitis [49]. Hence, early ERCP in biliary SAP is recommended only for documented or suspected cholangitis.

Newer Modalities

In view of the potential ominous outcomes of SAP and the unavailability of specific treatment, several experimental therapies have been attempted recently. One such therapy is surgical decompression of abdominal compartment syndrome (ACS). ACS is defined as an intra-abdominal pressure greater than 20 mm Hg with new-onset OF. In SAP, ACS is usually an early event, is seen in up to 60% of patients, and is associated with deterioration of multiple organ dysfunction syndrome. While ACS often results from retroperitoneal edema, fluid collections, ascites, and ileus; it may also be iatrogenic (from overaggressive fluid therapy). Besides conservative management, surgical decompression of the abdomen has been shown to improve ACS in several small studies [50].

Another experimental modality that was recently published as a case series is intra-abdominal vacuum-assisted closure after necrosectomy [51]. This technique might have a role in preventing ACS and reducing the time to definitive closure after necrosectomy.

It has been shown that patients with SAP have low serum levels of activated protein C (APC). However, a recent randomized, double-blind, placebo-controlled pilot trial using APC in ICU patients with SAP did not find any difference in SOFA scores, ventilator-free days, renal replacement–free days, vasopressor-free days, or days alive outside ICU between APC-treated and placebo-treated patients. No increase in bleeding-related complications was seen in APC-treated patients; however, these patients had increased levels of serum bilirubin in [52].

In experimental models of acute pancreatitis, use of pentoxifylline was shown to significantly reduce inflammatory cytokines, pancreatic histologic damage, bacterial translocation, and pancreatic infections. Currently, a randomized, double-blind, placebo-controlled trail of pentoxiphylline is being conducted in patients with SAP at the Mayo Clinic, Rochester, MN.

Conclusions

Considerable development has occurred in the understanding and management of SAP. However, a definitive management strategy is lacking, and many of the currently used modalities are controversial. The current prognostication tools are by no means perfect and have possibly reached their maximum utility, therefore mandating development of newer tools that should be guided by the dynamic parameters of the disease. Even though the proposed nomenclature of the revised Atlanta Classification by the International Working Group has generated robust enthusiasm among clinicians, many of the new terms need to be validated and consensus established among radiologists and clinicians before extrapolating them to the individual patient. Besides trying to clarify the existing controversies in the management of SAP, researchers should also focus on identifying newer targets and tailoring definitive therapy.

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